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MULTIPLE HETEROATOM CONTAINING HETEROCYCLIC RING COMPOUNDS SUBSTITUTED WITH CARBOXYLIC ACIDS AND ISOSTERES THEREOF

Inventors: Gregory S. Hamilton
Mark H. Norman
Yong-Qian Wu
Jia-He Li
Joseph P. Steiner

NATH & ASSOCIATES
1030 Fifteenth Street, N.W.
Sixth Floor
Washington, D.C. 20005
202-775-8383

MULTIPLE HETEROATOM CONTAINING HETEROCYCLIC RING COMPOUNDS SUBSTITUTED WITH CARBOXYLIC ACIDS AND ISOSTERES THEREOF

Related Application Data

This application is a continuation-in-part of U.S. patent application serial number 60/087,843 to Hamilton et al., entitled "Carboxylic Acids and Carboxylic Acid Isosteres of Heterocyclic Ring Compounds Having Multiple Heteroatoms", filed June 3, 1998.

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to novel carboxylic acids and isosteres of heterocyclic ring compounds which have multiple heteroatoms within the heterocyclic ring, novel derivatives of these carboxylic acids and isosteres containing N-linked diketos, sulfonamides, ureas and carbamates attached thereto, and their preparation and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, as well as for treating alopecia and promoting hair growth.

2. Description of Related Art

It has been found that picomolar concentrations of an immunosuppressant such as FK506 and rapamycin stimulate neurite outgrowth in PC12 cells and sensory neurons, namely dorsal root ganglion cells (DRGs). Lyons et al., *Proc. of Natl. Acad. Sci.*, 1994 vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury and results in functional recovery in animals with sciatic nerve lesions.

Several neurotrophic factors affecting specific neuronal populations in the central nervous system have been

identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat Alzheimer's patients with exogenous nerve growth factor or other neurotrophic proteins such as brain derived nerve factor (BDNF), glial derived nerve factor, ciliary neurotrophic factor, and neurotropin-3 to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressants exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., 1991, J. Am. Soc. Nephrol. 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina such as non-localized headaches (De Groen et al., 1987, N. Engl. J. Med. 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., 1989 N. Engl. J. Med. 321: 1725).

Accordingly, there is a need for small-molecule compounds which are useful for providing neurotrophic effects and for treating neurodegenerative disorders.

Hair loss occurs in a variety of situations. These situations include male pattern alopecia, alopecia senilis, alopecia areata, diseases accompanied by basic skin lesions or tumors, and systematic disorders such as nutritional disorders and internal secretion disorders. The mechanisms causing hair loss are very complicated, but in some instances can be attributed to aging, genetic disposition, the activation of male hormones, the loss of blood supply to hair

follicles, and scalp abnormalities.

The immunosuppressant drugs FK506, rapamycin and cyclosporin are well known as potent T-cell specific immunosuppressants, and are effective against graft rejection after organ transplantation. It has been reported that topical, but not oral, application of FK506 (Yamamoto et al., J. Invest. Dermatol., 1994, 102, 160-164; Jiang et al., J. Invest. Dermatol. 1995, 104, 523-525) and cyclosporin (Iwabuchi et al., J. Dermatol. Sci. 1995, 9, 64-69) stimulates hair growth in a dose-dependent manner. One form of hair loss, alopecia areata, is known to be associated with autoimmune activities; hence, topically administered immunomodulatory compounds are expected to demonstrate efficacy for treating that type of hair loss. The hair growth stimulating effects of FK506 have been the subject of an international patent filing covering FK506 and structures related thereto for hair growth stimulation (Honbo et al., EP 0 423 714 A2). Honbo et al. discloses the use of relatively large tricyclic compounds, known for their immunosuppressive effects, as hair revitalizing agents.

The hair growth and revitalization effects of FK506 and related agents are disclosed in many U.S. patents (Goulet et al., U.S. Patent No. 5,258,389; Luly et al., U.S. Patent No. 5,457,111; Goulet et al., U.S. Patent No. 5,532,248; Goulet et al., U.S. Patent No. 5,189,042; Ok et al., U.S. Patent No. 5,208,241; Rupprecht et al., U.S. Patent No. 5,284,840; and Organ et al., U.S. Patent No. 5,284,877). These patents claim FK506 related compounds. Although they do not claim methods of hair revitalization, they disclose the known use of FK506 for effecting hair growth. Similar to FK506 (and the claimed variations in the Honbo et al. patent), the compounds claimed in these patents are relatively large. Further, the cited patents relate to immunomodulatory compounds for use in autoimmune related diseases, for which FK506's efficacy is well known.

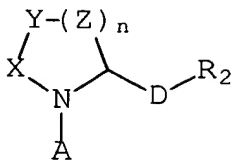
Other U.S. patents disclose the use of cyclosporin and related compounds for hair revitalization (Hauer et al., U.S. Patent No. 5,342,625; Eberle, U.S. Patent No. 5,284,826; and Hewitt et al., U.S. Patent No. 4,996,193). These patents also relate to compounds useful for treating autoimmune diseases and cite the known use of cyclosporin and related immunosuppressive compounds for hair growth.

However, immunosuppressive compounds by definition suppress the immune system and also exhibit other toxic side effects. Accordingly, there is a need for small molecule compounds which are useful as hair revitalizing compounds.

SUMMARY OF THE INVENTION

The present invention is directed to novel carboxylic acids and isosteres of heterocyclic ring compounds which have multiple (i.e. two or more) heteroatoms within the heterocyclic ring, novel derivatives of these carboxylic acids and isosteres containing N-linked diketos, sulfonamides, ureas and carbamates attached thereto, and their preparation and use for treating neurological disorders including physically damaged nerves and neurodegenerative diseases, as well as for treating alopecia and promoting hair growth. These compounds stimulate neuronal regeneration and outgrowth and as such are useful for treating neurological disorders and neurodegenerative diseases. These compounds also promote hair growth and as such are useful for treating hair loss disorders. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity and/or are non-immunosuppressive.

A preferred embodiment of this invention is a compound having the formula (I):



(I)

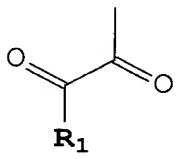
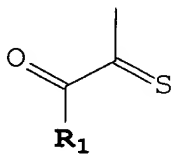
where

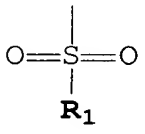
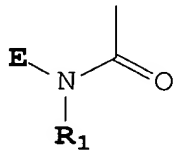
X, Y, and Z are independently selected from the group consisting of C, O, S, or N, provided that X, Y, and Z are not all C;

n is 1-3;

A is selected from the group consisting of L_1, L_2, L_3, or L_4,

where

L_1 is  , L_2 is  ,

L_3 is  , and L_4 is  ,

R_1 and E are independently selected from the group consisting of hydrogen, C_1-C_9 straight or branched chain alkyl or alkenyl, C_2-C_9 straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, and heterocycle;

D is selected from the group consisting of a bond, C_1-C_{10} straight or branched chain alkyl, ethylene, and butylene;

R_2 is carboxylic acid or a carboxylic acid isostere;

wherein said alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or carboxylic acid isostere is optionally substituted with one or more substituents selected from R^3, where

R^3 is hydroxy, halo, haloalkyl, thiocarbonyl, alkoxy, alkenoxy, alkylaryloxy, aryloxy, arylalkyloxy, cyano, nitro, imino, alkylamino, aminoalkyl, sulfhydryl, thioalkyl, alkylthio, sulfonyl, C_1-C_6 straight or branched chain alkyl,

C_2-C_6 straight or branched chain alkenyl or alkynyl, aryl, heteroaryl, carbocycle, heterocycle, or CO_2R^4 where R^4 is hydrogen or C_1-C_9 straight or branched chain alkyl or alkenyl; or a pharmaceutically acceptable salt, ester, or solvate thereof;

provided that:

R_1 is not substituted with both hydroxy and oxygen to form carboxy, or R_1 is not substituted with both alkoxy and oxygen to form alkoxycarbonyl, or R_1 is not substituted with both amine and oxygen to form amide;

further provided that:

when A is L_1 or L_2, and D is a bond,

then R_2 is not COOH, or an amide;

further provided that:

when A is L_1, and R_1 is methyl, and D is a bond,

then R_2 is not COOH;

further provided that:

when A is L_3, and R_1 is phenyl, methylphenyl, phenylmethyl, substituted or unsubstituted phenoxyphenyl, substituted naphthyl, or methoxyphenyl, and D is a bond,

then R_2 is not COOH or an amide;

further provided that:

when A is L_3, and R_1 is phenyl, and D is a bond,

then R_2 is not thiophenyl;

further provided that:

when A is L_3, and R_1 is phenyl, and D is oxyethyl,

then R_2 is not an amide;

further provided that:

when A is L_3, and R_1 is substituted isoquinoline, and D is butyl,

then R_1 is not an amide;

further provided that:

when A is L_3 or L_4, and R_1 is unsubstituted or substituted phenyl, and D is C_1-C_3 alkyl or alkenyl,

then R_1 is not COOH, OH, or an amide;

further provided that:

when A is L_4, and R_1 is phenyl, halo-substituted phenyl, dimethylphenyl, carboxy-substituted alkyl, substituted butyl, or methylphenyl, and D is a bond,

then R_2 is not COOH;

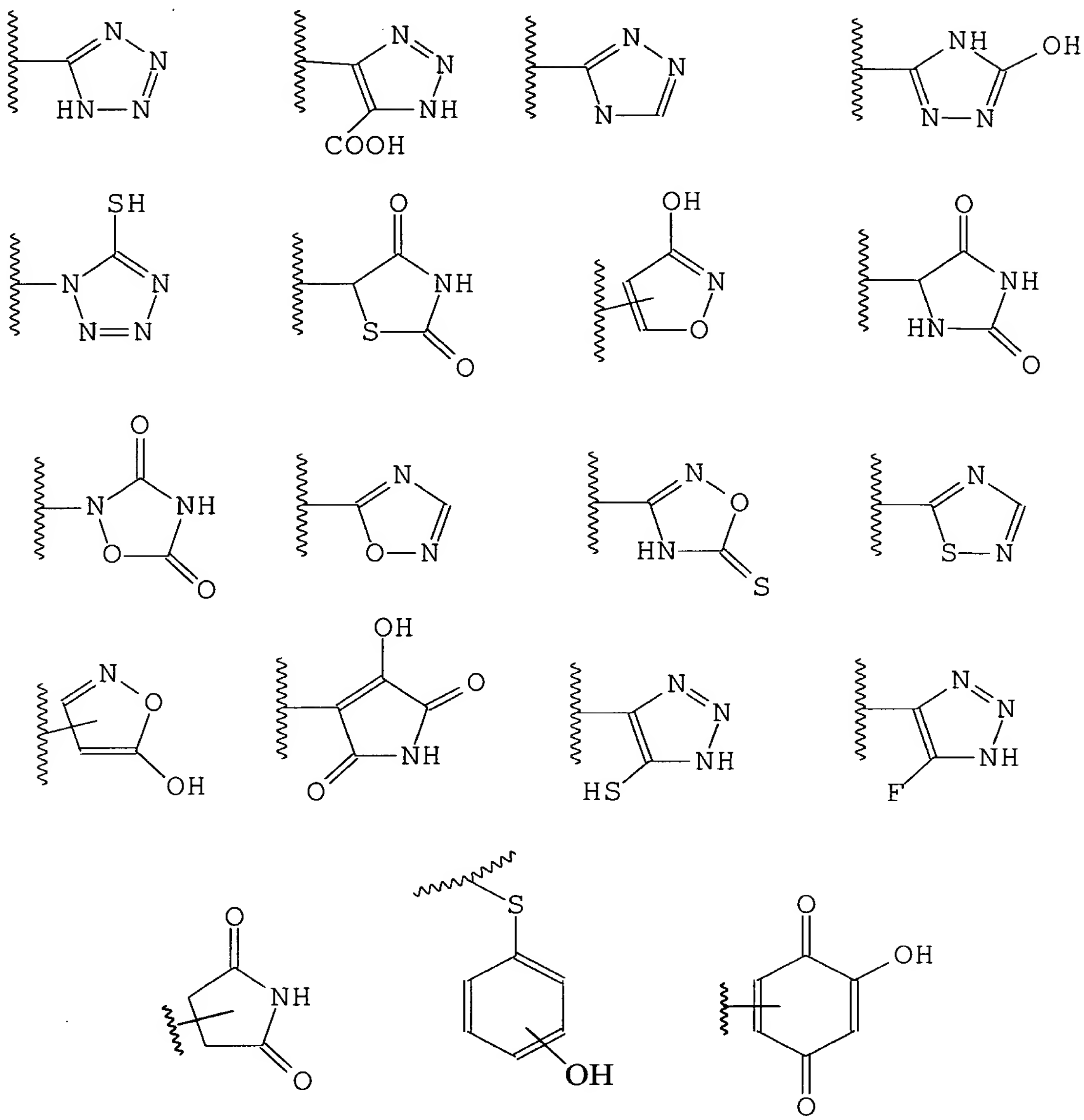
further provided that:

when A is L_4, and R_1 is cyano-substituted alkyl, and D is a bond,

then R_2 is not an amide.

Preferred embodiments of this invention are where R_2 is a carbocycle or heterocycle containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions with R^3.

Especially preferred embodiments of this invention are where R_2 is selected from the group below:



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3.

Another preferred embodiment of this invention is where R_2 is selected from the group consisting of $-COOH$, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, $-CN$, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$, $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$, $-COHNSO_2R^3$, and $-CONR^3CN$.

Preferred embodiments of this invention are the neurotrophic compounds (2S)-1-(phenylmethyl)carbamoyl-2-hydroxymethyl (4-thiazolidine); (2S)-1-(1,1-dimethyl propyl)carbamoyl-2-(4-thiazolidine)tetrazole; and (2S)-1-(phenylmethyl) carbamoyl-2-(4-thiazolidine) carbonitrile.

Another preferred embodiment of this invention is a pharmaceutical composition containing: an effective amount of a compound of formula (I); and a pharmaceutically suitable or acceptable carrier. For neurotrophic compositions a neurotrophic factor different from formula (I) may also be administered or otherwise included in the composition.

Another preferred embodiment of the invention is a method of promoting neuronal regeneration and growth in mammals, comprising administering to a mammal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

Another preferred embodiment of the invention is a method of treating a neurological disorder in an animal, comprising administering to an animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring to stimulate growth of damaged peripheral nerves or to promote neuronal regeneration.

Yet another preferred embodiment of the invention is a method of preventing neurodegeneration in an animal, comprising administering to an animal an effective amount of

a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

Yet another preferred embodiment of the invention is a method of treating alopecia or promoting hair growth in an animal, comprising administering to an animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a photograph of C57 Black 6 mice before being shaved for the hair regeneration experiment.

Figure 2 is a photograph of mice treated with a vehicle after six weeks. Figure 2 shows that less than 3% of the shaved area is covered with new hair growth when the vehicle (control) is administered.

Figure 3 is a bar graph illustrating relative hair growth on shaved mice treated with N-heterocyclic carboxylic acids or carboxylic acid isosteres at 1μmole per milliliter three times per week. Hair growth was evaluated after 14 days of treatment.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" means a branched or unbranched saturated hydrocarbon chain comprising a designated number of carbon atoms. For example, a C_1-C_6 straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms, and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. It is also contemplated as within the scope of the present invention that "alkyl" may also refer to a hydrocarbon chain wherein any of the carbon atoms of said

alkyl are optionally replaced with O, NH, S, or SO_2. For example, carbon 2 of n-pentyl can be replaced with O to form propyloxymethyl.

"Alkenyl" means a branched or unbranched unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C_2-C_6 straight or branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like. It is also contemplated as within the scope of the present invention that "alkenyl" may also refer to an unsaturated hydrocarbon chain wherein any of the carbon atoms of said alkenyl are optionally replaced with O, NH, S, or SO_2. For example, carbon 2 of 4-pentene can be replaced with O to form (2-propene)oxymethyl.

"Alkoxy" means the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms.

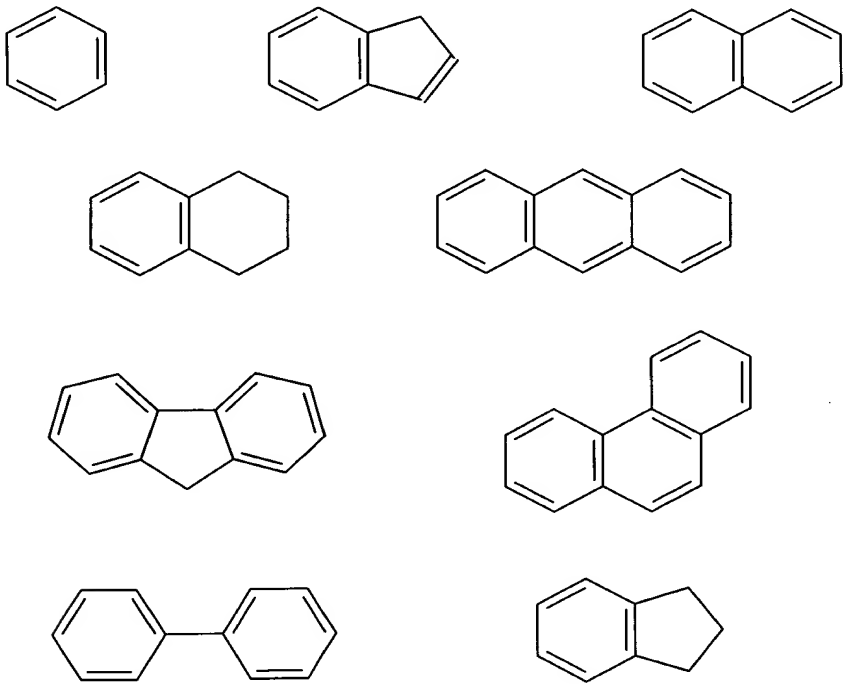
The term "carbocycle" refers to an organic cyclic moiety in which the cyclic skeleton is comprised of only carbon atoms whereas the term "heterocycle" refers to an organic cyclic moiety in which the cyclic skeleton contains one or more heteroatoms selected from the group comprising nitrogen, oxygen, or sulfur and which may or may not include carbon atoms.

Thus, the term "carbocycle" refers to a carbocyclic moiety containing the indicated number of carbon atoms. The term "C_3-C_8 cycloalkyl", therefore, refers to an organic cyclic substituent in which three to eight carbon atoms form a three, four, five, six, seven, or eight-membered ring, including, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl ring. As used herein, "carbocycle" may also refer to two or more cyclic ring systems which are fused to form, for example

bicyclic, tricyclic, or other similar bridged substituents (e.g. adamantyl).

"Aryl" refers to an aromatic carbocyclic group having a single ring, for example a phenyl ring; multiple rings, for example biphenyl; or multiple condensed rings in which at least one ring is aromatic, for example naphthyl, 1,2,3,4-tetrahydronaphthyl, anthryl, or phenanthryl, which can be unsubstituted or substituted with one or more other substituents as defined above. The substituents attached to a phenyl ring portion of an aryl moiety in the compounds of Formula (I) may be configured in the ortho-, meta-, or para-orientations.

Examples of typical aryl moieties included in the scope of the present invention may include, but are not limited to, the following:



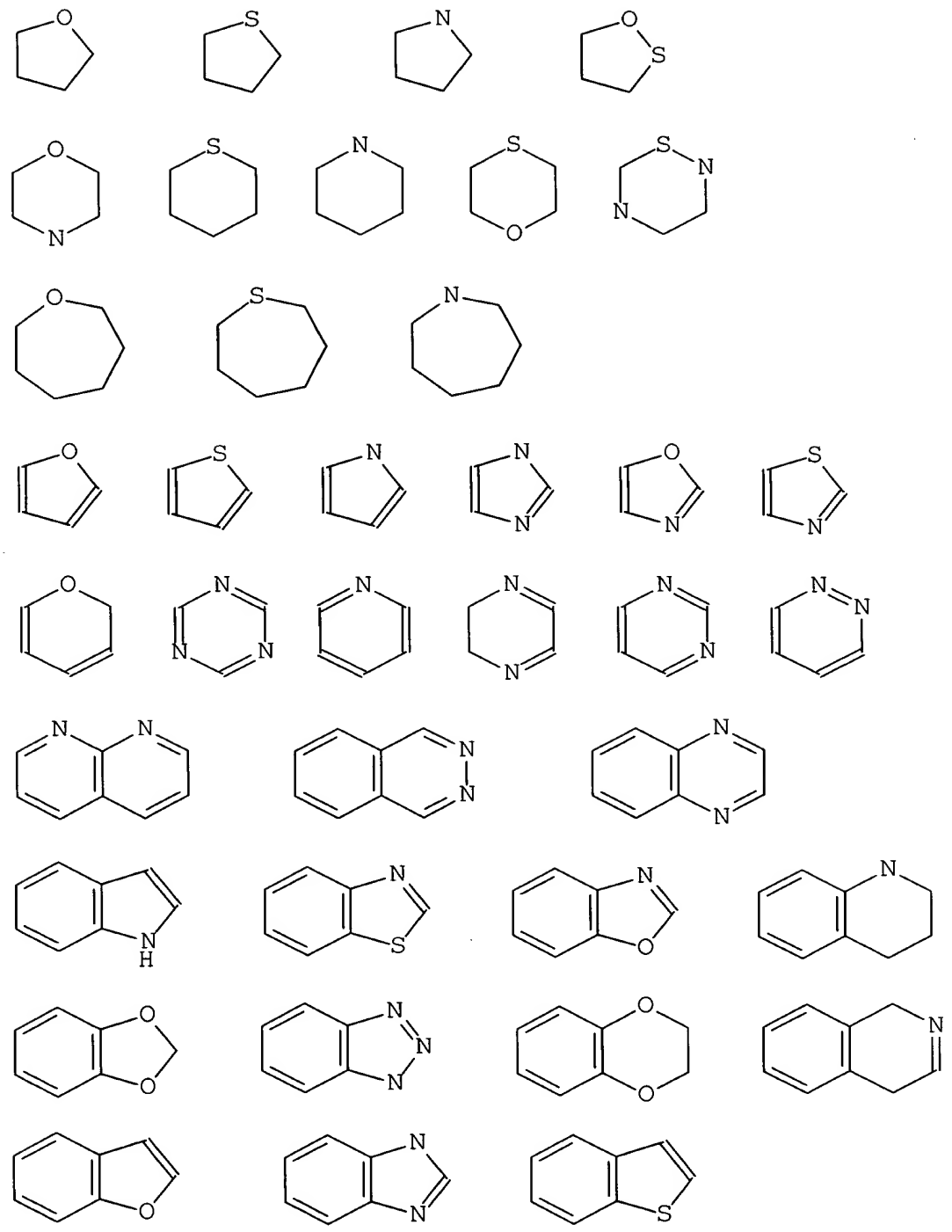
"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring, multiple rings, or multiple condensed rings, and having at least one hetero atom such as nitrogen, oxygen, or sulfur within at

least one of the rings. "Heteroaryl" refers to a heterocycle in which at least one ring is aromatic. Any of the heterocyclic or heteroaryl groups can be unsubstituted or optionally substituted with one or more groups as defined above. Further, bi- or tri-cyclic heteroaryl moieties may comprise at least one ring which is either completely or partially saturated.

As one skilled in the art will appreciate, such heterocyclic moieties may exist in several isomeric forms, all of which are encompassed by the present invention. For example, a 1,3,5-triazine moiety is isomeric to a 1,2,4-triazine group. Such positional isomers are to be considered within the scope of the present invention. Likewise, the heterocyclic or heteroaryl groups can be bonded to other moieties in the compounds of the present invention. The point(s) of attachment to these other moieties is not to be construed as limiting on the scope of the invention. Thus, by way of example, a pyridyl moiety may be bound to other groups through the 2-, 3-, or 4-position of the pyridyl group. All such configurations are to be construed as within the scope of the present invention.

"Aralkyl" refers to alkyl or alkylene (alkenyl) chain which is substituted with aryl, heteroaryl, carbocycle or heterocycle, or alternatively one or more aryl, heteroaryl, carbocycle, or heterocycle(s) which is/are substituted with alkyl or alkenyl, i.e. 'Alkyl/alkylene which is substituted with Ar' or 'Ar which is substituted with alkyl/alkylene'.

Examples of heterocyclic or heteroaryl moieties included in the scope of the present invention may include, but are not limited to, the following:



"Halo" means at least one fluoro, chloro, bromo, or iodo moiety.

The term "pharmaceutically acceptable salt, ester, or solvate" refers to salt, ester, or solvates of the subject

compounds which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. The salt, ester, or solvates can be formed with inorganic or organic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, naphthylate, 2-naphthalenesulfonate, nicotinate, oxalate, sulfate, thiocyanate, tosylate and undecanoate. Base salt, ester, or solvates include ammonium salts, alkali metal salts such as lithium, sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salt with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quarternized with such agents as: 1) lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; 2) dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; 3) long chain alkyls such as decyl, lauryl, myristyl and stearyl substituted with one or more halide such as chloride, bromide and iodide; and 4) aryl or arylalkyl halides like benzyl and phenethyl bromide and others.

The compounds of this invention may possess at least one asymmetric center and thus can be produced as mixtures of stereoisomers or as individual enantiomers or diastereomers. The individual stereoisomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolution of the compound of formula (I). It is understood that the individual stereoisomers as well as mixtures (racemic and non-racemic)

of stereoisomers are encompassed by the scope of the present invention. The S-stereoisomer at atom 1 of formula I is a most preferred embodiment of the invention.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

"Isomers" are different compounds that have the same molecular formula and includes cyclic isomers such as (iso)indole and other isomeric forms of cyclic moieties.

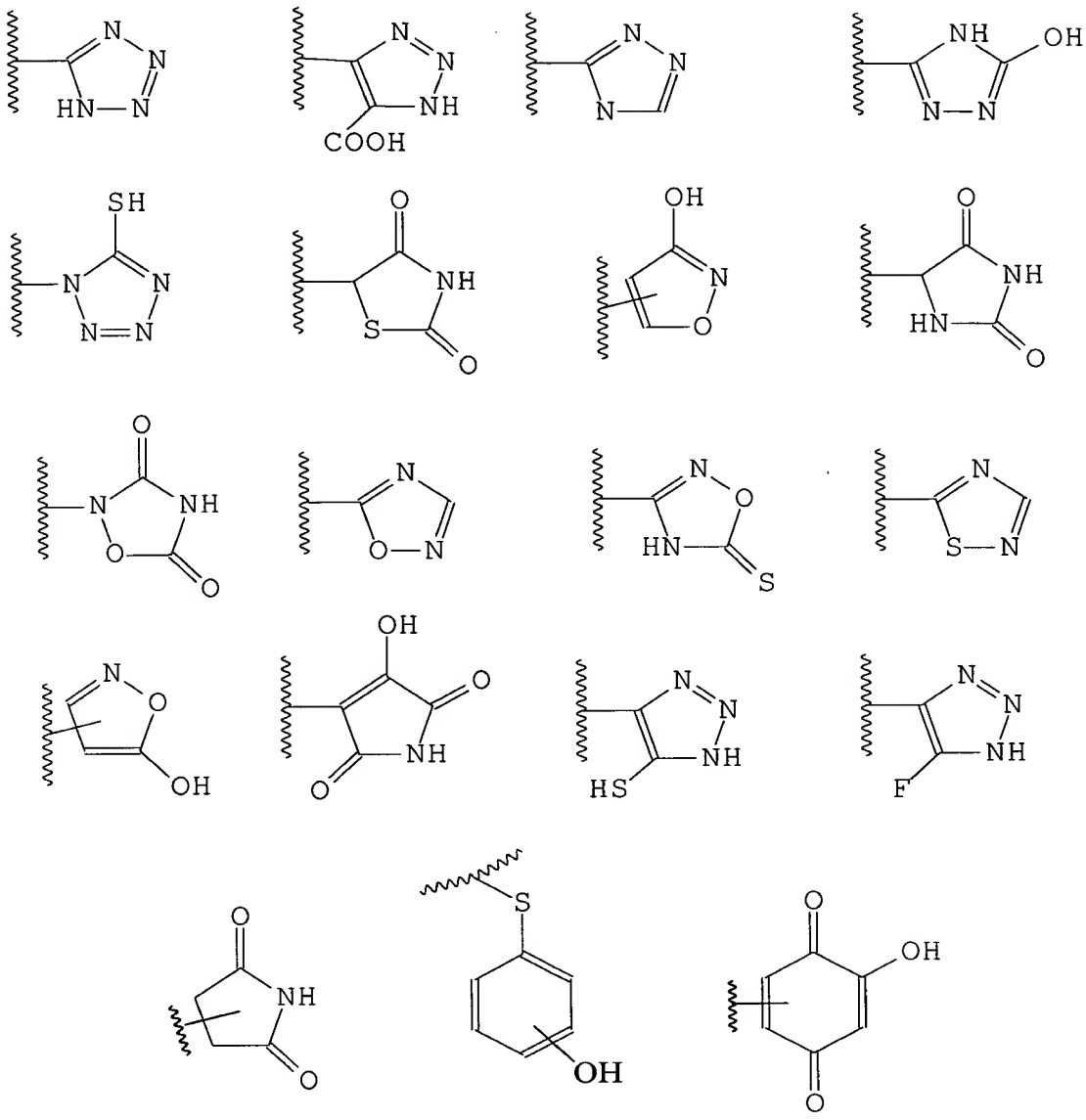
"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other.

"Diastereoisomers" are stereoisomers which are not mirror images of each other.

"Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Isosteres" are different compounds that have different molecular formulae but exhibit the same or similar properties. For example, tetrazole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have very different molecular formulae. Tetrazole is one of many possible isosteric replacements for carboxylic acid. Other carboxylic acid isosteres contemplated by the present invention include $-COOH$, $-SO_3H$, $-SO_2HNR^3$, $-PO_2(R^3)_2$, $-CN$, $-PO_3(R^3)_2$, $-OR^3$, $-SR^3$, $-NHCOR^3$, $-N(R^3)_2$, $-CON(R^3)_2$, $-CONH(O)R^3$, $-CONHNHSO_2R^3$, $-COHNSO_2R^3$, and $-CONR^3CN$.

In addition, carboxylic acid isosteres can include 5-7 membered carbocycles or heterocycles containing any combination of CH_2, O, S, or N in any chemically stable oxidation state, where any of the atoms of said ring structure are optionally substituted in one or more positions. The following structures are non-limiting examples of preferred carbocyclic and heterocyclic isosteres contemplated by this invention.



where the atoms of said ring structure may be optionally substituted at one or more positions with R^3. The present invention contemplates that when chemical substituents are added to a carboxylic isostere then the inventive compound retains the properties of a carboxylic isostere.

The present invention contemplates that when a carboxylic isostere is optionally substituted with one or more moieties selected from R^3, then the substitution cannot eliminate the carboxylic acid isosteric properties of the inventive compound. The present invention contemplates that the placement of one or more R^3 substituents upon a carbocyclic or heterocyclic carboxylic acid isostere shall not be at an atom(s) which maintains or is integral to the carboxylic acid isosteric properties of the inventive compound if such a substituent(s) would destroy the carboxylic acid isosteric properties of the inventive compound.

Other carboxylic acid isosteres not specifically exemplified or described in this specification are also contemplated by the present invention.

The system used in naming the compounds of the present invention is shown below, using a compound of formula I as an example.

A compound of the present invention, especially formula I, wherein n is 1, X is O, D is a bond, R_1 is 1,1,dimethylpropyl, and R_2 is -CN, is named (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarbonitrile.

"Alopecia" refers to deficient hair growth and partial or complete loss of hair, including without limitation androgenic alopecia (male pattern baldness), toxic alopecia, alopecia senilis, alopecia areata, alopecia pelada and trichotillomania. Alopecia results when the pilar cycle is disturbed. The most frequent phenomenon is a shortening of the hair growth or anagen phase due to cessation of cell proliferation. This results in an early onset of the catagen

phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. Alopecia has a number of etiologies, including genetic factors, aging, local and systemic diseases, febrile conditions, mental stresses, hormonal problems, and secondary effects of drugs.

"Pilar cycle" refers to the life cycle of hair follicles, and includes three phases:

(1) the anagen phase, the period of active hair growth which, insofar as scalp hair is concerned, lasts about three to five years;

(2) the catagen phase, the period when growth stops and the follicle atrophies which, insofar as scalp hair is concerned, lasts about one to two weeks; and

(3) the telogen phase, the rest period when hair progressively separates and finally falls out which, insofar as scalp hair is concerned, lasts about three to four months.

Normally 80 to 90 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. In the telogen phase, hair is uniform in diameter with a slightly bulbous, non-pigmented root. By contrast, in the anagen phase, hair has a large colored bulb at its root.

The term "preventing neurodegeneration" as used herein includes the ability to inhibit or prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease, or at risk of developing a new degenerative disease and for inhibiting or preventing further neurodegeneration in patients who are already suffering from or have symptoms of a neurodegenerative disease when the compounds are given concurrently.

"Promoting hair growth" refers to maintaining, inducing, stimulating, accelerating, or revitalizing the germination of

hair.

The term "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

(i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease and/or condition, i.e., arresting its development; or

(iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

"Treating alopecia" refers to:

(i) preventing alopecia in an animal which may be predisposed to alopecia; and/or

(ii) inhibiting, retarding or reducing alopecia; and/or

(iii) promoting hair growth; and/or

(iv) prolonging the anagen phase of the hair cycle; and/or

(v) converting vellus hair to growth as terminal hair. Terminal hair is coarse, pigmented, long hair in which the bulb of the hair follicle is seated deep in the dermis. Vellus hair, on the other hand, is fine, thin, non-pigmented short hair in which the hair bulb is located superficially in the dermis. As alopecia progresses, the hairs change from the terminal to the vellus type.

The term "neurotrophic" as used herein includes without limitation the ability to stimulate neuronal regeneration or growth and/or the ability to prevent or treat neurodegeneration.

The term "non-immunosuppressive" refers to the inability of the compounds of the present invention to trigger an immune response when compared to a control such as FK506 ro cyclosporin A. Assays for determining immunosuppression are well known to those of ordinary skill in the art. Specific

non-limiting examples of well known assays include PMA and OKT3 assays wherein mitogens are used to stimulate proliferation of human peripheral blood lymphocytes (PBC). Compounds added to such assay systems are evaluated for their ability to inhibit such proliferation.

Compounds of the Invention

The present invention relates to the surprising discovery that carboxylic acid or carboxylic acid isostere compounds are neurotrophic and are able to treat alopecia. Accordingly, a novel class of compounds are provided. A preferred feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity.

Preferred compounds of the present invention contain carboxylic acid moieties and other isosteric replacements for carboxylic acid moieties, of which several examples are specified herein. Other isosteric replacements for carboxylic acid moieties, known to those skilled in the art of medicinal chemistry, are within the scope of the invention if not otherwise specified.

The neurotrophic compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for treatment of various mammalian neurological disorders.

The novel compounds of the present invention possess an excellent degree of neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and in the treatment of several neurological disorders known to be associated with neuronal

degeneration and peripheral neuropathies. The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia, glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathic such as those caused by lead, dapsone, ticks, prophyria, or Gullain-Barré syndrome, Alzheimer's disease, and Parkinson's disease.

The above discussion relating to the utility and administration of the compounds of the present invention also applies to the pharmaceutical compositions of the present invention.

The term "pharmaceutically acceptable carrier" as used herein refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbent, preservative, surfactant, colorant, flavorant, or sweetener.

For these purposes the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion techniques.

For oral administration, the compounds of the present invention may be provided in any suitable dosage form known in the art. For example, the compositions may be incorporated into tablets, powders, granules, beads, chewable lozenges, capsules, liquids, aqueous suspensions or

solutions, or similar dosage forms, using conventional equipment and techniques known in the art. Tablet dosage forms are preferred. Tablets may contain carriers such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.

When preparing dosage forms incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbents, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants, such as sodium lauryl sulfate, polysorbate 80, and the like; colorants such as F.D.& C. dyes and lakes; flavorants; and sweeteners.

Compositions and methods of the invention also may utilize controlled release technology. Thus, for example, the inventive compounds may be incorporated into a hydrophobic polymer matrix for controlled release over a period of days. Such controlled release films are well known to the art. Particularly preferred are transdermal delivery systems. Other examples of polymers commonly employed for this purpose that may be used in the present invention include nondegradable ethylene-vinyl acetate copolymer and degradable lactic acid-glycolic acid copolymers which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly(vinylalcohol) also may be useful, but for shorter release cycles then the other polymer releases systems, such as those mentioned above.

To be effective therapeutically as central nervous system targets, the compounds of the present invention should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route or other appropriate delivery system suitable for administration to the brain.

The compounds of the present invention may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

The compounds of this invention may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The compounds of this invention may also be administered

topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas.

For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively for the ophthalmic uses the compounds may be formulated in an ointment such as petrolatum.

For topical application to the skin, the compounds can be formulated in a suitable ointment containing the compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated in a suitable lotion or cream containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application for the lower intestinal tract an be effected in a rectal suppository formulation (see above) or in a suitable enema formulation.

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the

host treated and the particular mode of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

To effectively treat alopecia or promote hair growth, the compounds used in the inventive methods and pharmaceutical compositions must readily affect the targeted areas. For these purposes, the compounds are preferably administered topically to the skin.

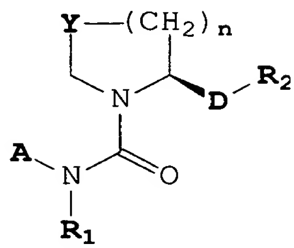
For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds can be administered with other hair revitalizing agents. Specific dose levels for the other hair revitalizing agents will depend upon the factors previously stated and the effectiveness of the drug combination. Other routes of administration known in the pharmaceutical art are

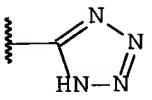
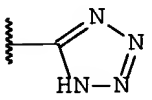
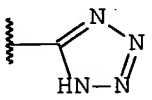
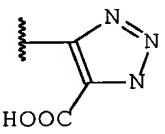
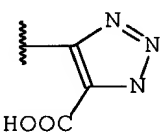
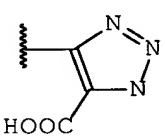
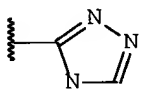
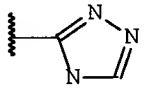
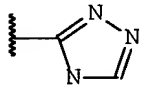
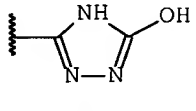
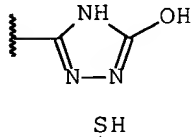
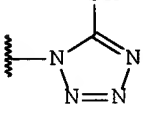
also contemplated by this invention.

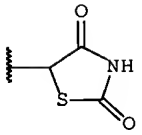
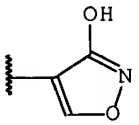
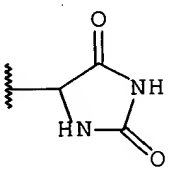
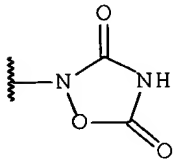
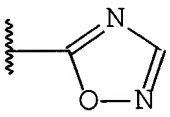
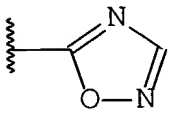
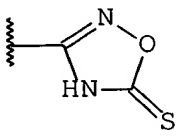
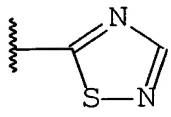
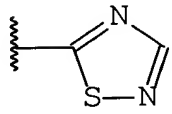
Specific embodiments of the inventive compounds are presented in Tables I, II, and III. The present invention contemplates employing the compounds of Tables I, II and III, below, for use in compositions and methods to prevent and/or treat a neurological disorder in an animal, and for use in compositions and methods to treat alopecia and promote hair growth in an animal, and all other uses suggested in this specification.

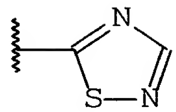
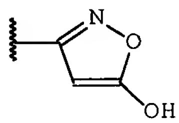
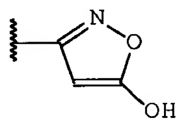
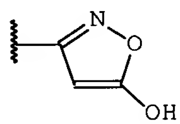
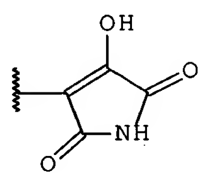
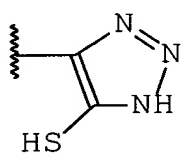
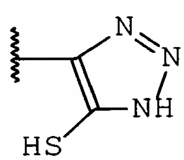
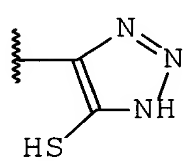
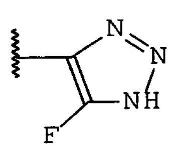
TABLE I



No.	n	D	R2	A	Y	R1
1	1	bond	COOH	H	S	Benzyl
2	1	bond	COOH	H	S	α-MethylBenzyl
3	1	bond	COOH	H	S	4-MethylBenzyl
4	1	bond	Tetrazole	H	S	Benzyl
5	1	bond	SO_3H	H	O	α-MethylBenzyl
6	1	CH_2	COOH	H	O	4-MethylBenzyl
7	1	bond	SO_2HNMe	H	O	Benzyl
8	1	bond	CN	H	N	α-MethylBenzyl
9	1	bond	PO_3H_2	H	N	4-MethylBenzyl
10	2	bond	COOH	H	N	Benzyl
11	2	bond	COOH	H	S	α-MethylBenzyl
12	2	bond	COOH	H	S	4-MethylBenzyl
13	2	bond	COOH	H	S	3,4,5-trimethoxy phenyl
14	2	bond	COOH	H	S	Cyclohexyl
15	2	bond	PO_2HEt	H	O	i-propyl
16	2	bond	$PO_3HPropyl$	H	O	ethyl
17	2	bond	$PO_3(Et)_2$	H	N	Methyl
18	2	bond	OMe	H	S	tert-butyl
19	2	bond	OEt	H	S	n-pentyl
20	2	bond	OPropyl	H	S	n-hexyl
21	1	bond	OButyl	H	O	Cyclohexyl
22	1	bond	OPentyl	H	N	cyclopentyl
23	1	bond	OHexyl	H	S	n-heptyl
24	1	bond	SMe	H	S	n-octyl
25	1	bond	SEt	H	O	n-nonyl
26	2	bond	SPropyl	H	N	2-indolyl
27	2	bond	SButyl	H	O	2-furyl
28	2	bond	NHCOMe	H	S	2-thiazolyl
29	2	bond	NHCOEt	H	S	2-thienyl
30	1	CH_2	$N(Me)_2$	H	N	2-pyridyl
31	1	$(CH_2)_2$	N(Me)Et	H	S	1,1-dimethylpropyl
32	1	$(CH_2)_3$	$CON(Me)_2$	H	O	1,1-dimethylpropyl
33	1	$(CH_2)_4$	CONHMe	H	N	1,1-dimethylpropyl
34	1	$(CH_2)_5$	CONHEt	H	S	1,1-dimethylpropyl
35	1	$(CH_2)_6$	CONHPropyl	H	S	1,1-dimethylpropyl

No.	n	D	R2	A	Y	R1
36	1	bond		CH_2	S	Hydrogen
37	1	bond		$(CH_2)_2$	S	Cyclohexyl
38	1	bond		$(CH_2)_3$	S	Adamantyl
39	1	bond		$(CH_2)_4$	S	Pentafluorobenzyl
40	1	bond		$(CH_2)_5$	O	3,4,5-trimethoxyphenyl
41	1	CH_2		$(CH_2)_6$	O	Phenyl
42	1	bond		CH_2	O	2-furyl
43	1	bond		$(CH_2)_2$	N	2-thienyl
44	1	bond		$(CH_2)_3$	N	2-thiazolyl
45	2	bond		$(CH_2)_4$	N	1,1-dimethylbutyl
46	2	bond		$(CH_2)_5$	S	Hydrogen
47	2	bond		$(CH_2)_6$	S	Hydrogen

No.	n	D	R2	A	Y	R1
48	2	bond		CH_2	S	3,4,5-trimethoxyphenyl
49	2	bond		$(CH_2)_2$	S	3,4,5-trimethoxyphenyl
50	2	bond		$(CH_2)_3$	O	Cyclohexyl
51	2	bond		$(CH_2)_4$	O	Cyclohexyl
52	2	bond		$(CH_2)_5$	N	Adamantyl
53	2	bond		$(CH_2)_6$	S	Adamantyl
54	2	bond		CH_2	S	Pentafluorobenzyl
55	2	bond		$(CH_2)_2$	S	Pentafluorobenzyl
56	1	bond		$(CH_2)_3$	O	Phenyl

No.	n	D	R2	A	Y	R1
57	1	bond		$(CH_2)_4$	N	Phenyl
58	1	bond		$(CH_2)_5$	S	2-furyl
59	1	bond		$(CH_2)_6$	S	2-furyl
60	1	bond		CH_2	O	2-thienyl
61	2	bond		$(CH_2)_2$	N	2-thienyl
62	2	bond		$(CH_2)_3$	O	2-thiazolyl
63	2	bond		$(CH_2)_4$	S	2-thiazolyl
64	2	bond		$(CH_2)_5$	S	1,1-dimethylbutyl
65	1	CH_2		$(CH_2)_6$	N	1,1-dimethylbutyl

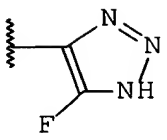
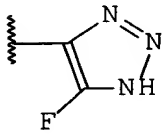
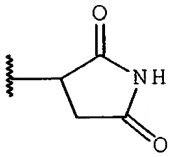
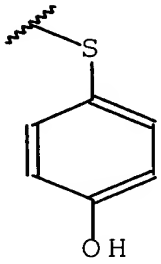
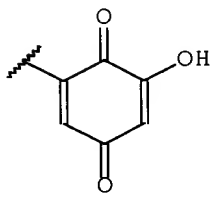
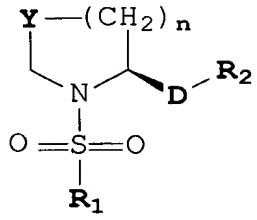
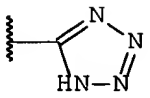
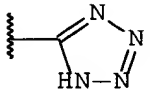
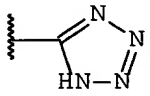
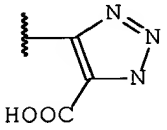
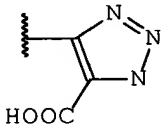
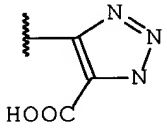
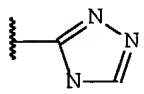
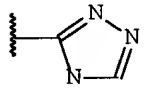
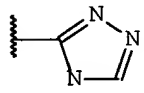
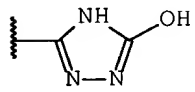
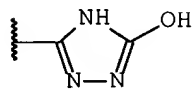
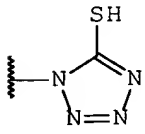
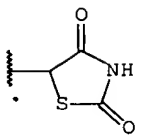
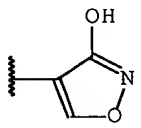
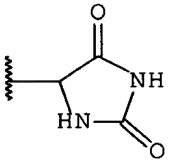
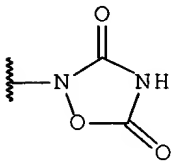
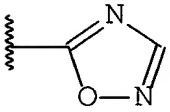
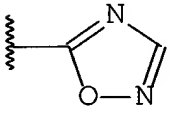
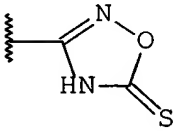
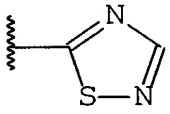
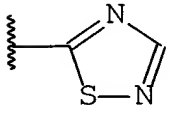
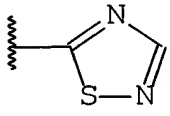
No.	n	D	R2	A	Y	R1
66	1	$(CH_2)_2$		CH_2	S	1,1-dimethylpropyl
67	1	$(CH_2)_3$		$(CH_2)_2$	O	1,1-dimethylpropyl
68	1	$(CH_2)_4$		$(CH_2)_3$	N	1,1-dimethylpropyl
69	1	$(CH_2)_5$		$(CH_2)_4$	S	1,1-dimethylpropyl
70	1	$(CH_2)_6$		$(CH_2)_5$	S	1,1-dimethylpropyl

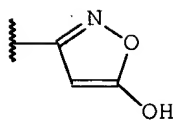
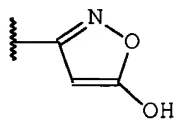
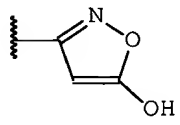
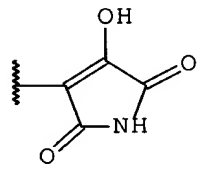
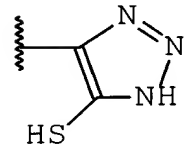
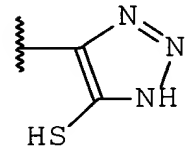
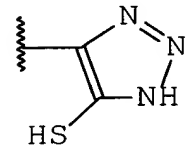
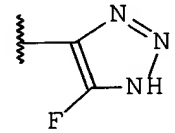
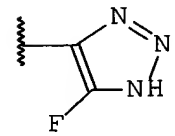
TABLE II



No.	n	D	R2	Y	R1
71	1	bond	CONH(O)Me	S	Benzyl
72	1	bond	CONH(O)Et	S	α-Methylphenyl
73	1	bond	CONH(O)Propyl	S	4-Methylphenyl
74	2	bond	COOH	S	Benzyl
75	2	bond	COOH	O	α-Methylphenyl
76	2	bond	COOH	O	4-Methylphenyl
77	1	CH_2	COOH	N	benzyl
78	1	$(CH_2)_2$	COOH	N	benzyl
79	1	$(CH_2)_3$	COOH	N	benzyl
80	1	$(CH_2)_4$	COOH	S	benzyl
81	1	$(CH_2)_5$	COOH	S	benzyl
82	1	$(CH_2)_6$	COOH	S	benzyl
83	1	$(CH_2)_7$	COOH	S	benzyl
84	1	$(CH_2)_8$	COOH	O	benzyl
85	1	$(CH_2)_9$	COOH	O	benzyl
86	1	$(CH_2)_{10}$	COOH	O	benzyl
87	1	C_2H_2	COOH	N	benzyl
88	1	2-OH,Et	COOH	N	benzyl
89	1	2butylene	COOH	S	benzyl
90	1	i-Pro	COOH	S	benzyl
91	1	tert-Bu	COOH	S	benzyl
92	1	2-nitro	COOH	S	benzyl
		Hexyl			
93	3	$(CH_2)_2$	CN	S	benzyl
94	1	$(CH_2)_3$	CN	S	benzyl
95	3	bond	$CONHNHSO_2Me$	N	Benzyl
96	3	bond	$CONHNHSO_2Et$	N	α-Methylphenyl
97	3	bond	$CONHSO_2Me$	N	4-Methylphenyl
98	2	bond	$CONHNHSO_2Et$	N	Phenyl
99	2	bond	CON(Me)CN	O	α-Methylphenyl
100	2	bond	CON(Et)CN	O	4-Methylphenyl
101	1	$(CH_2)_2$	COOH	O	methyl
102	1	$(CH_2)_3$	COOH	O	ethyl
103	1	$(CH_2)_4$	COOH	N	n-propyl
104	1	$(CH_2)_5$	COOH	N	t-butyl
105	1	$(CH_2)_6$	COOH	N	Pentyl
106	1	$(CH_2)_7$	COOH	S	Hexyl
107	1	$(CH_2)_8$	COOH	S	Septyl
108	1	$(CH_2)_9$	COOH	S	Octyl
109	1	$(CH_2)_{10}$	COOH	S	Nonyl

No.	n	D	R2	Y	R1
110	1	C_2H_2	COOH	S	Cyclohexyl
111	1	bond		S	Hydrogen
112	1	bond		S	Cyclohexyl
113	1	bond		S	Adamantyl
114	1	bond		S	Pentafluorobenzyl
115	1	bond		O	3,4,5-trimethoxyphenyl
116	1	CH_2		O	Phenyl
117	1	bond		O	2-furyl
118	1	bond		N	2-thienyl
119	1	bond		N	2-thiazolyl
120	2	bond		N	1,1-dimethylbutyl
121	2	bond		S	Hydrogen
122	2	bond		S	Hydrogen

No.	n	D	R2	Y	R1
123	2	bond		S	3,4,5-trimethoxyphenyl
124	2	bond		S	3,4,5-trimethoxyphenyl
125	2	bond		O	Cyclohexyl
126	2	bond		O	Cyclohexyl
127	2	bond		N	Adamantyl
128	2	bond		S	Adamantyl
129	2	bond		S	Pentafluorobenzyl
130	2	bond		S	Pentafluorobenzyl
131	1	bond		O	Phenyl
132	1	bond		N	Phenyl

No.	n	D	R2	Y	R1
133	1	bond		S	2-furyl
134	1	bond		S	2-furyl
135	1	bond		O	2-thienyl
136	2	bond		N	2-thienyl
137	2	bond		O	2-thiazolyl
138	2	bond		S	2-thiazolyl
139	2	bond		S	1,1-dimethylbutyl
140	1	CH_2		N	1,1-dimethylbutyl
141	1	$(CH_2)_2$		S	1,1-dimethylpropyl

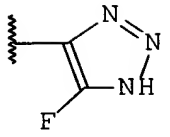
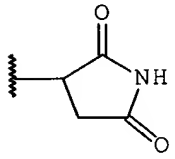
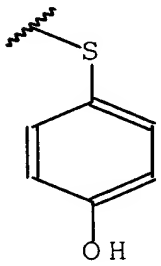
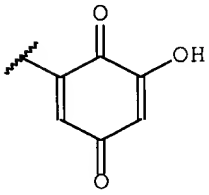
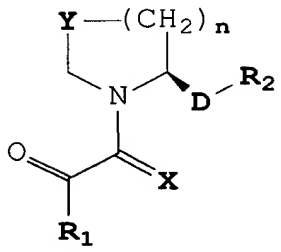
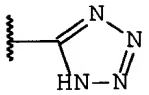
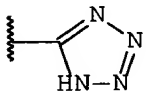
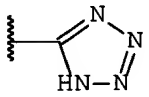
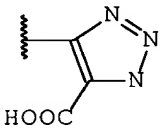
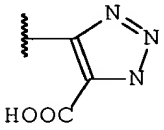
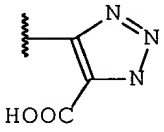
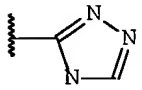
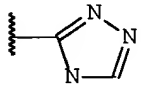
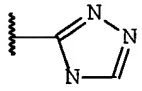
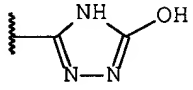
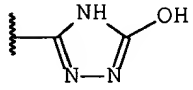
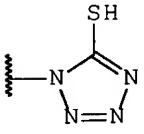
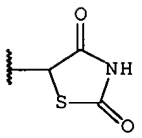
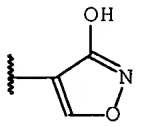
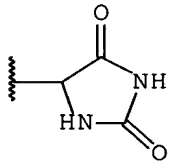
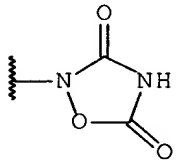
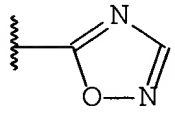
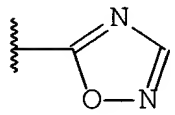
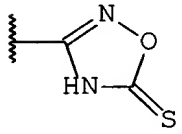
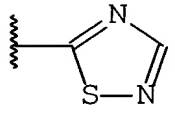
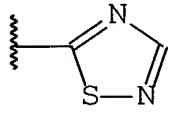
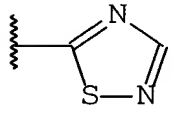
No.	n	D	R2	Y	R1
142	1	$(CH_2)_3$		O	1,1-dimethylpropyl
143	1	$(CH_2)_4$		N	1,1-dimethylpropyl
144	1	$(CH_2)_5$		S	1,1-dimethylpropyl
145	1	$(CH_2)_6$		S	1,1-dimethylpropyl

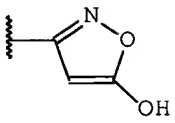
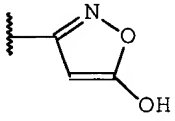
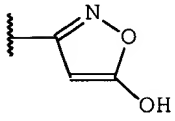
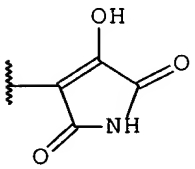
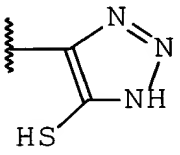
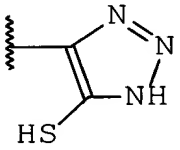
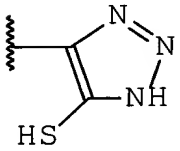
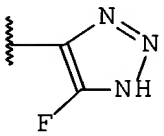
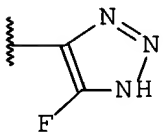
TABLE III

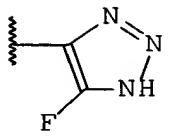
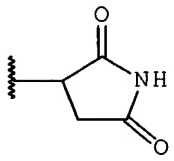
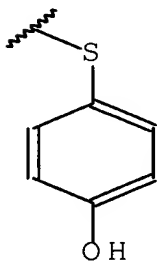
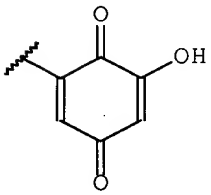


No.	n	X	D	R2	Y	R1
146	1	O	bond	CONH(O)Me	S	Benzyl
147	1	O	bond	CONH(O)Et	S	α-Methylphenyl
148	1	O	bond	CONH(O)Propyl	S	4-Methylphenyl
149	2	O	bond	COOH	S	Benzyl
150	2	O	bond	COOH	O	α-Methylphenyl
151	2	O	bond	COOH	O	4-Methylphenyl
152	1	O	CH_2	COOH	N	benzyl
153	1	O	$(CH_2)_2$	COOH	N	benzyl
154	1	O	$(CH_2)_3$	COOH	N	benzyl
155	1	O	$(CH_2)_4$	COOH	S	benzyl
156	1	O	$(CH_2)_5$	COOH	S	benzyl
157	1	O	$(CH_2)_6$	COOH	S	benzyl
158	1	O	$(CH_2)_7$	COOH	S	benzyl
159	1	O	$(CH_2)_8$	COOH	O	benzyl
160	1	O	$(CH_2)_9$	COOH	O	benzyl
161	1	O	$(CH_2)_{10}$	COOH	O	benzyl
162	1	O	C_2H_2	COOH	N	benzyl
163	1	O	2-OH,Et	COOH	N	benzyl
164	1	O	2butylene	COOH	S	benzyl
165	1	O	i-Pro	COOH	S	benzyl
166	1	S	tert-Bu	COOH	S	benzyl
167	1	S	2-nitro Hexyl	COOH	S	benzyl
168	3	S	$(CH_2)_2$	CN	S	benzyl
169	1	S	$(CH_2)_3$	CN	S	benzyl
170	3	S	bond	$CONHNHSO_2Me$	N	Benzyl
171	3	S	bond	$CONHNHSO_2Et$	N	α-Methylphenyl
172	3	S	bond	$CONHSO_2Me$	N	4-Methylphenyl
173	2	S	bond	$CONHNHSO_2Et$	N	Phenyl
174	2	S	bond	CON(Me)CN	O	α-Methylphenyl
175	2	S	bond	CON(Et)CN	O	4-Methylphenyl
176	1	S	$(CH_2)_2$	COOH	O	methyl
177	1	S	$(CH_2)_3$	COOH	O	ethyl
178	1	S	$(CH_2)_4$	COOH	N	n-propyl
179	1	S	$(CH_2)_5$	COOH	N	t-butyl
180	1	S	$(CH_2)_6$	COOH	N	Pentyl
181	1	S	$(CH_2)_7$	COOH	S	Hexyl
182	1	S	$(CH_2)_8$	COOH	S	Septyl
183	1	S	$(CH_2)_9$	COOH	S	Octyl

No.	n	X	D	R2	Y	R1
184	1	S	$(CH_2)_{10}$	COOH	S	Nonyl
185	1	S	C_2H_2	COOH	S	Cyclohexyl
186	1	O	bond		S	Hydrogen
187	1	O	bond		S	Cyclohexyl
188	1	O	bond		S	Adamantyl
189	1	O	bond		S	Pentafluorobenzyl
190	1	O	bond		O	3,4,5-trimethoxyphenyl
191	1	O	CH_2		O	Phenyl
192	1	O	bond		O	2-furyl
193	1	O	bond		N	2-thienyl
194	1	O	bond		N	2-thiazolyl
195	2	O	bond		N	1,1-dimethylbutyl
196	2	O	bond		S	Hydrogen
197	2	O	bond		S	Hydrogen

No.	n	X	D	R2	Y	R1
198	2	O	bond		S	3,4,5-trimethoxyphenyl
199	2	O	bond		S	3,4,5-trimethoxyphenyl
200	2	O	bond		O	Cyclohexyl
201	2	O	bond		O	Cyclohexyl
202	2	O	bond		N	Adamantyl
203	2	S	bond		S	Adamantyl
204	2	S	bond		S	Pentafluorobenzyl
205	2	S	bond		S	Pentafluorobenzyl
206	1	S	bond		O	Phenyl
207	1	S	bond		N	Phenyl

No.	n	X	D	R2	Y	R1
208	1	S	bond		S	2-furyl
209	1	S	bond		S	2-furyl
210	1	S	bond		O	2-thienyl
211	2	S	bond		N	2-thienyl
212	2	S	bond		O	2-thiazolyl
213	2	S	bond		S	2-thiazolyl
214	2	S	bond		S	1,1-dimethylbutyl
215	1	S	CH_2		N	1,1-dimethylbutyl
216	1	S	$(CH_2)_2$		S	1,1-dimethylpropyl

No.	n	X	D	R2	Y	R1
217	1	S	$(CH_2)_3$		O	1,1-dimethylpropyl
218	1	S	$(CH_2)_4$		N	1,1-dimethylpropyl
219	1	S	$(CH_2)_5$		S	1,1-dimethylpropyl
220	1	S	$(CH_2)_6$		S	1,1-dimethylpropyl

Compounds 221-440 are also exemplified in the present invention, and are defined as where Y is located at the 3-position of the heterocyclic ring for compounds 1-220, and n, A, D, Y, X, R_1, and R_2 remain the same as defined for compounds 1-220 in Tables I, II, and III.

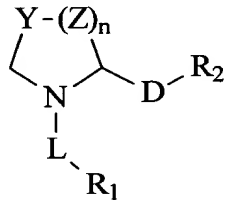
Exemplary compound 441 is defined where S is located at the 3-position of the heterocyclic ring (3-thiazolidine), n is 1, R_1 is 1,1-dimethylpropyl, D is a bond, R_2 is COOH.

Exemplary compound 442 is defined where O is located at the 2-position of the heterocyclic ring (2-oxopentanoyl), n is 1, R_1 is 1,1-dimethylpropyl, D is a bond, R_2 is COOH (i.e. 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid).

The present invention also contemplates other ring locations for the heteroatoms O, N, and S in neurotrophic heterocyclic compounds. Also contemplated by the present invention are neurotrophic heterocycles containing 3 or more heteroatoms chosen independently from O, N, and S.

Additional claimed or comparative carboxylic acids and isosteres of N-heterocyclic compounds which also show the remarkable neurotrophic and hair growth effects of the present invention are shown below in Table IV:

TABLE IV



Cpd.	n	D	R_2	L	R_1
A	1	bond	COOH	SO_2	Benzyl
B	1	bond	$CONH_2$	SO_2	Benzyl
C	1	bond	-CN	SO_2	Benzyl
D	1	bond	tetrazole	SO_2	Benzyl
E	1	CH_2	-OH	SO_2	Benzyl
F	1	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl
G	2	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl
H	1	CH_2	OH	1,2-dioxoethyl	1,1-dimethylpropyl
I	1	bond	tetrazole	1,2-dioxoethyl	1,1-dimethylpropyl
J	1	bond	-CN	1,2-dioxoethyl	1,1-dimethylpropyl
K	2	bond	$CONH_2$	1,2-dioxoethyl	1,1-dimethylpropyl

where Y and Z are both carbon for compounds A-K,

L	1	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl
M	1	bond	COOH	1,2-dioxoethyl	1,1-dimethylpropyl

where Z is S for compound L or where Y is S for compound M.

Pharmaceutical Compositions of the Present Invention

The present invention relates to a pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or

carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring; and

(ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring for treating neurodegenerative diseases, neurological disorders, and nerve damage, or promoting nerve growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition comprising:

(i) an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring for treating alopecia or promoting hair growth in an animal; and

(ii) a pharmaceutically acceptable carrier.

The compounds can be administered with other neurotrophic agents such as neurotrophic growth factor, brain derived growth factor, glial derived growth factor, cilial neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotropin-3 and neurotropin 4/5. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

Methods of the Present Invention

The present invention relates to the use of any of the compounds seen in Tables I, II, III, and IV, any of the other compounds described above, and other compounds not specifically mentioned or described herein, in the preparation of a medicament for the treatment of a disease such as peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis. The present invention also relates to the use of carboxylic acid and carboxylic acid isostere compounds for treating the above-mentioned neuropathies, neurological disorders, and neurological damage.

The present invention also relates to a method for treating alopecia or promoting hair growth in an animal, which comprises administering to said animal an effective amount of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring. The present invention also relates to using the inventive compounds and compositions in the preparation of a medicament for the treatment of alopecia or promoting hair growth in an animal.

The inventive method is particularly useful for treating male pattern alopecia, alopecia senilis, alopecia areata, alopecia resulting from skin lesions or tumors, alopecia resulting from cancer therapy such as chemotherapy and radiation, and alopecia resulting from systematic disorders such as nutritional disorders and internal secretion disorders.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease or disorder being treated and form of administration.

MPTP Model of Parkinson's Disease in Mice

MPTP lesioning of dopaminergic neurons in mice is used as an animal model of Parkinson's Disease. Four week old male CD1 white mice are dosed i.p. with 30 mg/kg of MPTP for 5 days. Test compounds (4 mg/kg), or vehicle, are administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days following cessation of MPTP treatment. At 18 days following MPTP treatment, the animals are sacrificed and the striata dissected and perfusion-fixed. Immunostaining is performed on saggital and coronal brain sections using anti-tyrosine hydroxylase 1 g to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle, a substantial loss of functional dopaminergic terminals is observed as compared to non-lesioned animals. Lesioned animals receiving test compounds show a significant recovery of TH-stained dopaminergic neurons. This model presents quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving the compounds of the present invention.

Table V presents the percent recovery of dopaminergic neurons in the first (concurrent dosing) paradigm in animals receiving (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-3-thiazolidine-2-carboxylic acid as well as claimed or comparative compounds 443-448.

Table V, below, shows the remarkable neuroregenerative effects of carboxylic acid or carboxylic acid isostere related compounds illustrating the neurotrophic capability of carboxylic acid isosteres as a class showing that lesioned animals receiving the carboxylic acid or carboxylic acid isostere compounds provide a remarkable recovery of TH-stained dopaminergic neurons.

Table V - MPTP Neurodegenerative Model

	% Recovery
Compound A	24.4 %
Cmpds B-E	ND
Compound F	26.7 %
Compound G	ND
Compound H	23.2 %
Compound I	19.6 %
Compound J	34.1 %
Compound K	46.5 %
Compound L	14.0 %
Compound M	ND

Percent striatal innervation density was quantitated in brain sections with an anti-tyrosine hydroxylase immunoglobulin, which is indicative of functional dopaminergic neurons. The striatal innervation density of 23% for animals pretreated with only a vehicle and administered a vehicle orally during treatment, is indicative of normal non-lesioned striatal tissue. Striatal innervation density is reduced to 5% for animals pretreated with MPTP and administered a vehicle orally during treatment, and is indicative of MPTP-induced lesioning. Surprisingly, striatal innervation density is increased 8-13% for animals pretreated with MPTP and administered 0.4 mg/kg, orally during treatment, indicating substantial neuronal regeneration after induction of MPTP-derived lesions.

***In Vivo* Hair Generation Test With C57 Black 6 Mice**

C57 black 6 mice are used to demonstrate the hair revitalizing properties of the ureas and carbamates of N-heterocyclic carboxylic acids or carboxylic acid isosteres. Referring now to FIGS. 1 and 2 of the drawings, C57 black 6 mice, approximately 7 weeks old, had an area of about 2 inches by 2 inches on their hindquarters shaved to remove all existing hair. Care was taken not to nick or cause abrasion

to the underlaying dermal layers. The animals were in anagen growth phase, as indicated by the pinkish color of the skin. Referring now to FIG. 2, four animals per group were treated by topical administration with 20% propylene glycol vehicle (FIG. 2), or related compounds dissolved in the vehicle. The animals were treated with vehicle or N-heterocyclic carboxylic acids or isosteres every 48 hours (3 applications total over the course of 5 days) and the hair growth was allowed to proceed for 6 weeks. Hair growth was quantitated by the percent of shaved area covered by new hair growth during this time period.

FIG. 2 shows that animals treated with vehicle exhibited only a small amount of hair growth in patches or tufts, with less than 3% of the shaved area covered with new growth.

In contrast, FIG. 3 shows that animals treated for 2 weeks with the N-heterocyclic carboxylic acid compounds i.e. compound F, compound G, and compound K exhibited dramatic hair growth, covering greater than 25% of the shaved area in all animals for two of the compounds.

FIG. 3 shows the relative hair growth on shaven C57 black 6 mice 14 days after being treated with N-heterocyclic carboxylic acids or carboxylic acid isosteres. The mice had a 2 x 2 inch region on their backside shaved to remove all hair. Care was taken not to nick or cause abrasion to the underlying dermal layers. Compounds at a concentration of 1 µmole per milliliter were carefully applied to the shaved area of the mice (5 mice per group) three times per week. Hair growth was evaluated 14 days after initiation of drug treatment. The relative scale for assessing hair growth is as follows:

0 = no growth;

1 = beginning of growth in small tufts;

2 = hair growth covering over <25% of shaved area;

3 = hair growth covering over >25% of shaved area, but less than 50% of shaved area;

4 = hair growth covering over >50% of shaved area, but less than 75% of shaved area;

5 = complete hair growth of shaved area.

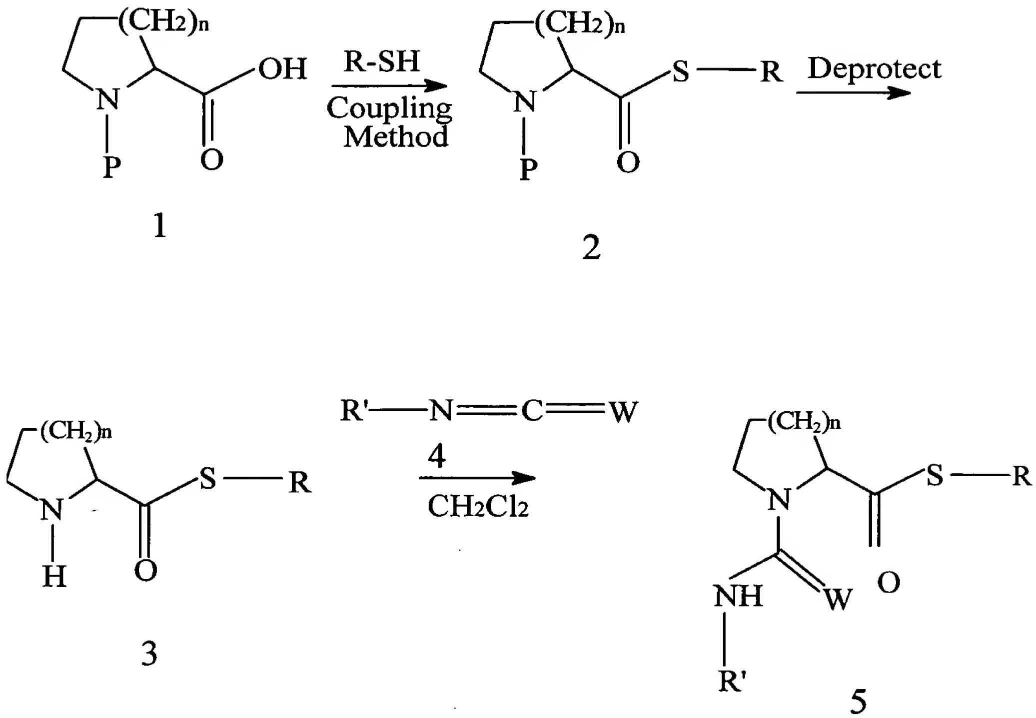
The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

SYNTHETIC SCHEMES

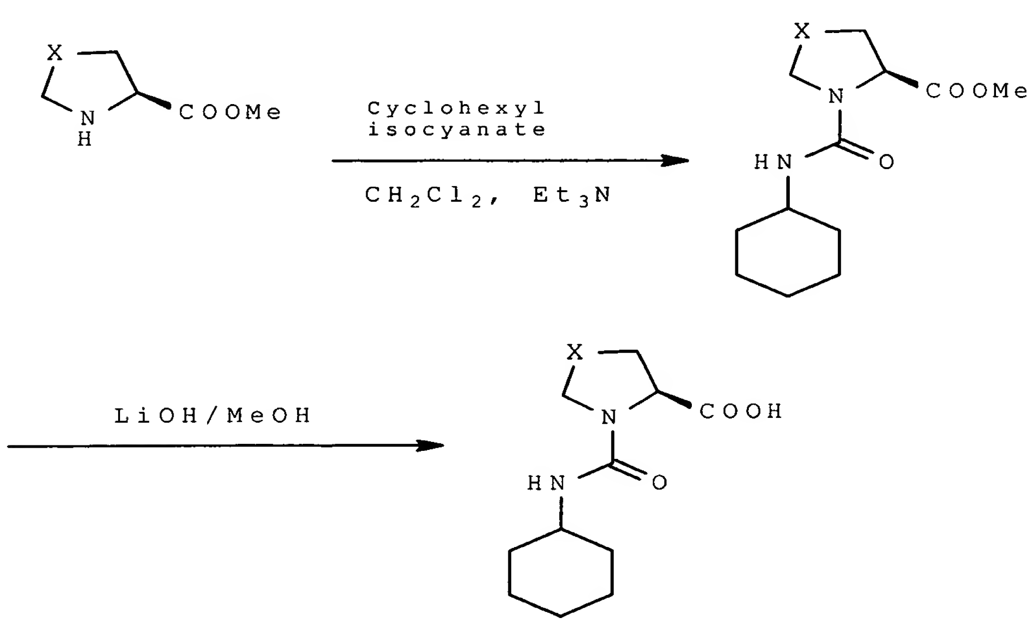
The novel compounds of this invention may be readily prepared by standard techniques of organic chemistry, utilizing the general synthetic pathways depicted below for diketo derivatives, sulfonamide derivatives, and urea or carbamate derivatives.

Cyclic amino acids **1** protected by suitable blocking groups P on the amino acid nitrogen may be reacted with thiols RSH to generate thioesters **2**. After removal of the protecting group, the free amine **3** may be reacted with a variety of isocyanates or isothiocyanates to provide final ureas or thioureas, respectively.

SCHEME I

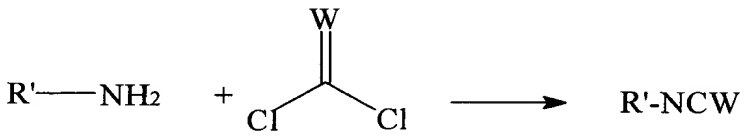


Another scheme for preparing ureas or carbamates is set forth below.



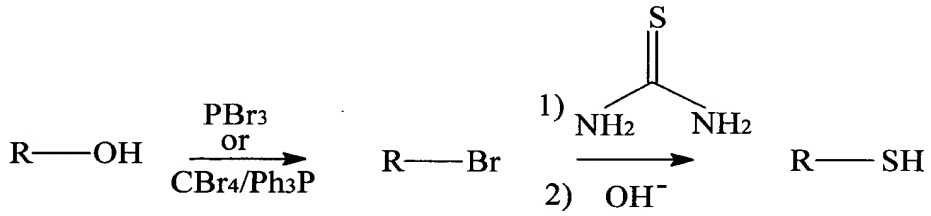
SCHEME II

Isocyanates (R'NCO) or isothiocyanates (R'NCS) **4** may be conveniently prepared from the corresponding readily available amines by reaction with phosgene or thiophosgene, as depicted below.



SCHEME III

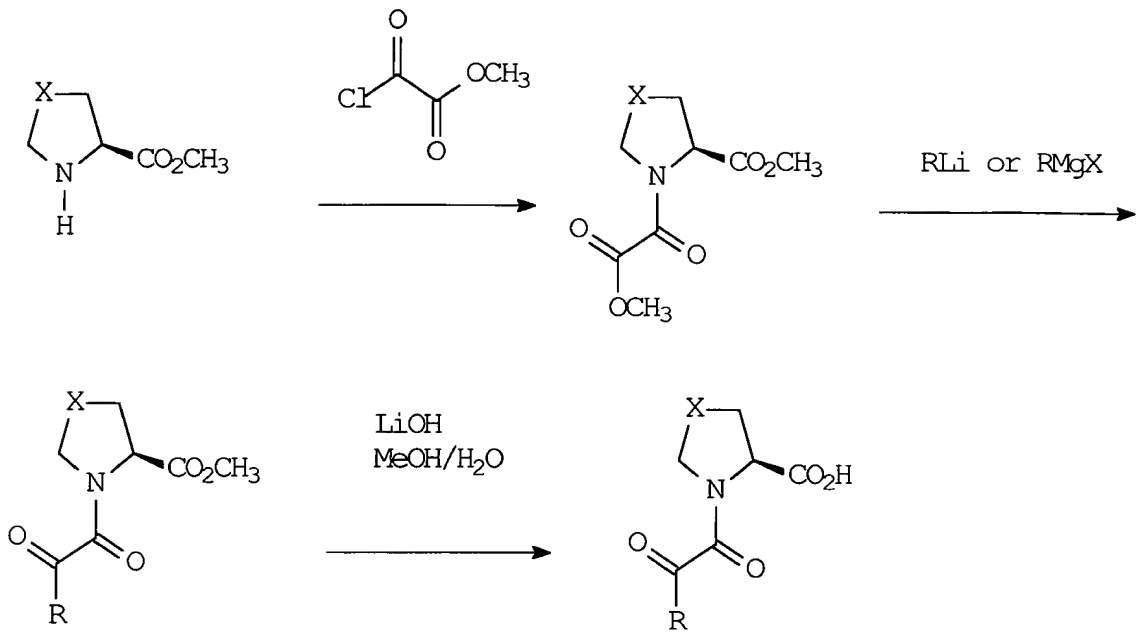
Thiols R-SH may be conveniently prepared from the corresponding readily available alcohols or halides via a two step replacement of halide by sulfur, as described below. Halides may be reacted with thiourea, and the corresponding alkyl thiouronium salts hydrolyzed to provide thiols RSH. If alcohols are used as the starting materials, they may be first converted to the corresponding halides by standard methods.



SCHEME IV

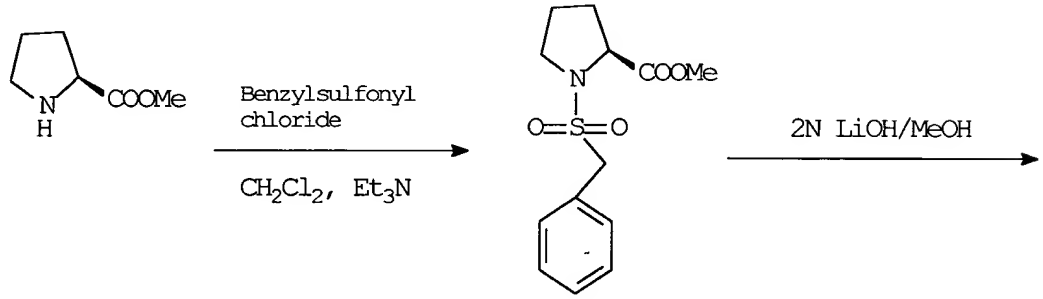
N-glyoxylproline derivatives may be prepared by reacting L-proline methyl ester with methyl oxalyl chloride as shown below. The resulting oxamates may be reacted with a variety of carbon nucleophiles to obtain compounds of the present invention or useful for preparing

compounds of the present invention.

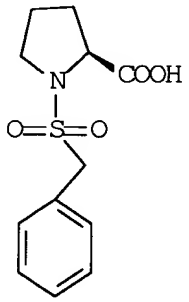


SCHEME V

Synthetic schemes for preparing sulfonamide derivatives are known in the art and compounds of the present invention may be synthesized using schemes such as are set forth

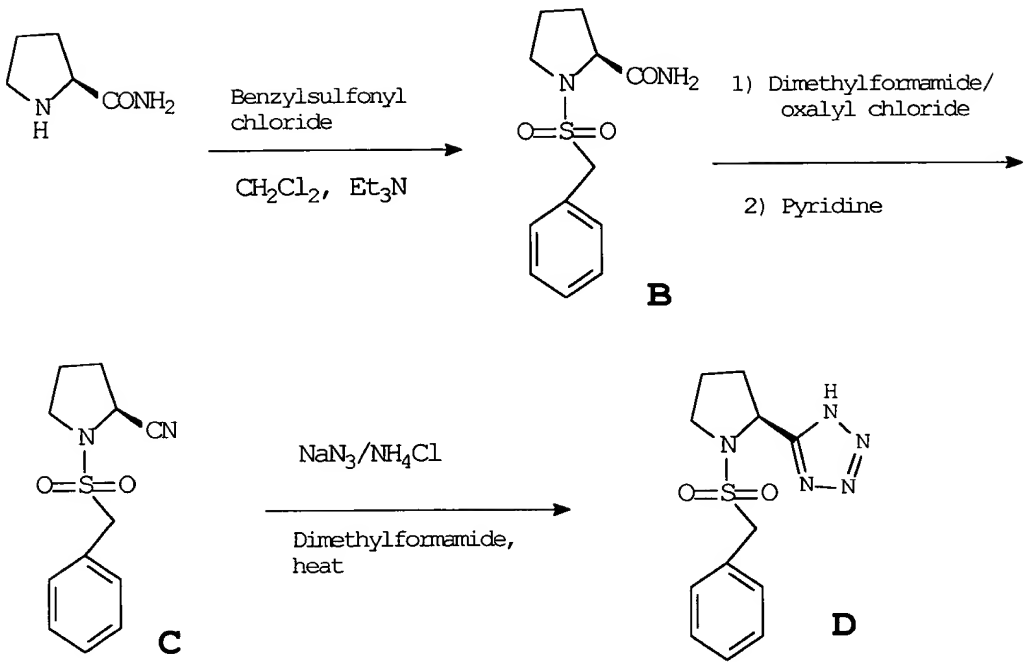


below.



A

SCHEME VI



SCHEME VII

Examples

The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise specified, all percentages are based on 100% by weight of the final compound.

EXAMPLE 1

Synthesis of 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid (4) (Compound 190).

Methyl 1,3-oxazolidine-4-carboxylate (1) was synthesized according to the procedure found in J. Med. Chem., 1990, 33, 1459-1469.

Methyl 2-[4-(methoxycarbonyl)(1,3-oxazolidin-3-yl)]-2-oxoacetate (2). To an ice cooled solution of methyl 1,3-oxazolidine-4-carboxylate (1) (0.65 g, 4.98 mM) were added triethylamine (0.76 ml, 5.45 mM) and methyl oxalyl

chloride (0.5 ml, 5.45 mM). This mixture was stirred at 0°C for 2 hours. After this time the mixture was washed with water, then brine, dried with anhydrous magnesium sulfate, filtered and evaporated. The resulting pale yellow oil was flash chromatographed eluting with 30% EtOAc/hexane, 50% EtOAc/hexane, and finally 75% EtOAc/hexane. A clear oil of product (0.52 g, 48%) was obtained. Anal. ($C_8H_{11}NO_6$)C,H,N.

^{1}H NMR ($CDCl_3$, 400 MHz): d (2 rotamers 1:1) 3.78 (s, 1.5H); 3.79 (s, 1.5H); 3.87 (s, 1.5H); 3.91 (s, 1.5H); 4.14-4.36 (m, 2H); 4.70 (dd, 0.5H, J=4.1, 6.8); 5.08 (dd,0.5H, J=3.1,6.7); 5.10 (d, 0.5H, J=5.9); 5.27 (d, 0.5H, J=5.8); 5.36 (dd, 1H, J=5.3, 17.8).

Methyl 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylate (3).

To a solution of methyl 2-[4-(methoxycarbonyl)(1,3-oxazolidin-3-yl)]-2-oxoacetate (2) (0.84 g, 3.87 mM) in THF (50 ml) cooled to -78°C was added 1,1-dimethylpropylmagnesium chloride (1M in THF, 8ml, 8 mM). After 3 hrs. at -78°C the mixture was quenched with saturated NH_4Cl (50 ml) and extracted with ethyl acetate (100 ml). The organic layer separated, washed with brine (100 ml), dried with anhydrous magnesium sulfate, filtered and evaporated. The resulting pale yellow oil was flash chromatographed eluting with 20% EtOAc/hexane. A clear oil (3) (0.61 g, 61%) was obtained.

^{1}H NMR ($CDCl_3$, 400 MHz): d 0.85 (t, 3H, J=7.5); 1.25 (s, 3H); 1.26 (s, 3H); 1.67-1.94 (m, 2H); 3.79 (s, 3H); 4.12-4.31 (m, 2H); 4.64 (dd, 1H, J=4.1, 6.8); 5.04 (dd, 2H, J=4.9, 9.4).

3-(3,3-dimethyl-2-oxopentanoyl)-1,3-oxazolidine-4-carboxylic acid (4).

Dissolved methyl 3-(3,3-dimethyl-2-oxopentanoyl)-1,3-

oxazolidine-4-carboxylate (3) (0.6 g, 2.33 mM) in MeOH (25 ml) and added LiOH (1M in water, 10 ml, 10 mM). Stirred this mixture overnight at room temperature. Evaporated and partitioned the residues between EtOAc (50 ml) and 2N HCl (50 mL). Extracted the aqueous layer twice more with EtOAc (2 x 25 ml). Combined extracts, washed with brine (50 ml), dried with anhydrous magnesium sulfate, filtered and evaporated. A clear oil product (0.49 g, 86%) was obtained. Anal. ($C_{11}H_{17}NO_5$) C, H, N.

^{1}H NMR ($CDCl_3$, 400 MHz): d 0.84 (t, 3H, J=7.5); 1.25 (s, 6H); 1.70-1.95 (m, 2H); 4.22-4.29 (m, 2H); 4.66 (dd, 1H, J=4.6, 6.5); 5.04 (dd, 2H, J=5.0, 8.9); 7.67 (bs, 1H).

Example 2

A lotion comprising the following composition may be prepared.

	(%)
95% Ethanol	80.0
a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	10.0
α-Tocopherol acetate	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
purified water	9.0
perfume and dye	q.s.

Into 95% ethanol are added a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, α-tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume and a dye. The resulting mixture is stirred and dissolved, and purified water is added to the mixture to obtain a transparent liquid lotion.

5 ml of the lotion may be applied once or twice per day to a site having marked baldness or alopecia.

Example 3

A lotion comprising the following composition shown may be prepared.

	(%)
95% Ethanol	80.0
a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.005
Hinokitol	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
Purified water	19.0
Perfume and dye	q.s.

Into 95% ethanol are added a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, hinokitol, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye. The resulting mixture is stirred, and purified water is added to the mixture to obtain a transparent liquid lotion.

The lotion may be applied by spraying once to 4 times per day to a site having marked baldness or alopecia.

Example 4

An emulsion may be prepared from A phase and B phase having the following compositions.

(A phase)	(%)
Whale wax	0.5
Cetanol	2.0
Petrolatum	5.0

Squalane	10.0
Polyoxyethylene (10 mole) monostearate	2.0
Sorbitan monooleate	1.0
A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.01
(B phase)	(%)
Glycerine	10.0
Purified water	69.0
Perfume, dye, and preservative	q.s.

The A phase and the B phase are respectively heated and melted and maintained at 80°C. Both phases are then mixed and cooled under stirring to normal temperature to obtain an emulsion.

The emulsion may be applied by spraying once to four times per day to a site having marked baldness or alopecia.

Example 5

A cream may be prepared from A phase and B phase having the following compositions.

(A Phase)	(%)
Fluid paraffin	5.0
Cetostearyl alcohol	5.5
Petrolatum	5.5
Glycerine monostearate	33.0
Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0
Propylparaben	0.3
(B Phase)	(%)

a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.8
Glycerine	7.0
Dipropylene glycol	20.0
Polyethylene glycol 4000	5.0
Sodium Hexametaphosphate	0.005
Purified water	44.895

The A phase is heated and melted, and maintained at 70°C. The B phase is added into the A phase and the mixture is stirred to obtain an emulsion. The emulsion is then cooled to obtain a cream.

The cream may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 6

A liquid comprising the following composition may be prepared.

	(%)
Polyoxyethylene butyl ether	20.0
Ethanol	50.0
A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	0.001
Propylene glycol	5.0
Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
Perfume	q.s.
Purified water	q.s.

Into ethanol are added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a carboxylic acid or carboxylic acid isostere of an N-

heterocyclic ring compound having two or more heteroatoms in the ring, and perfume. The resulting mixture is stirred, and purified water is added to the mixture to obtain a liquid.

The liquid may be applied once to 4 times per day to a site having marked baldness or alopecia.

Example 7

A shampoo comprising the following composition may be prepared.

	(%)
Sodium laurylsulfate	5.0
Triethanolamine laurylsulfate	5.0
Betaine lauryldimethylaminoacetate	6.0
Ethylene glycol distearate	2.0
Polyethylene glycol	5.0
a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring	5.0
Ethanol	2.0
Perfume	0.3
Purified water	69.7

Into 69.7 of purified water are added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethyl-aminoacetate. Then a mixture obtained by adding 5.0 g of a carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, 5.0 g of polyethylene glycol, and 2.0 g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume are successively added. The resulting mixture is heated and subsequently cooled to obtain a shampoo.

The shampoo may be used on the scalp once or twice per day.

Example 8

A patient is suffering from alopecia senilis. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 9

A patient is suffering from male pattern alopecia. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 10

A patient is suffering from alopecia areata. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 11

A patient is suffering from hair loss caused by skin lesions. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 12

A patient is suffering from hair loss caused by tumors. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the

same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 13

A patient is suffering from hair loss caused by a systematic disorder, such as a nutritional disorder or an internal secretion disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 14

A patient is suffering from hair loss caused by chemotherapy. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same, may be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 15

A patient is suffering from hair loss caused by radiation. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring compound having two or more heteroatoms in the ring, or a pharmaceutical composition comprising the same may, be administered to the patient. Increased hair growth is expected to occur following treatment.

Example 16

A patient is suffering from a neurodegenerative disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or a pharmaceutical composition comprising the same is administered. It would be expected that the patient would improve their condition or recover.

Example 17

A patient is suffering from a neurological disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 18

A patient is suffering from stroke. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 19

A patient is suffering from Parkinson's Disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 20

A patient is suffering from Alzheimer's Disease. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 21

A patient is suffering from a peripheral neuropathy. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 22

A patient is suffering from amyotrophic lateral sclerosis. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions

comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 23

A patient is suffering from a spinal injury. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or pharmaceutical compositions comprising same is administered. It would be expected that the patient would improve their condition or recover.

Example 24

A patient is at risk of suffering from a neurodegenerative disease or neurological disorder. A carboxylic acid or carboxylic acid isostere of an N-heterocyclic ring or a pharmaceutical composition comprising the same is prophelactically administered. It would be expected that the patient would be prevented from some or all of the effects of the disease or disorder, or would significally improve their condition or recover over patients who were not pre-treated.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.